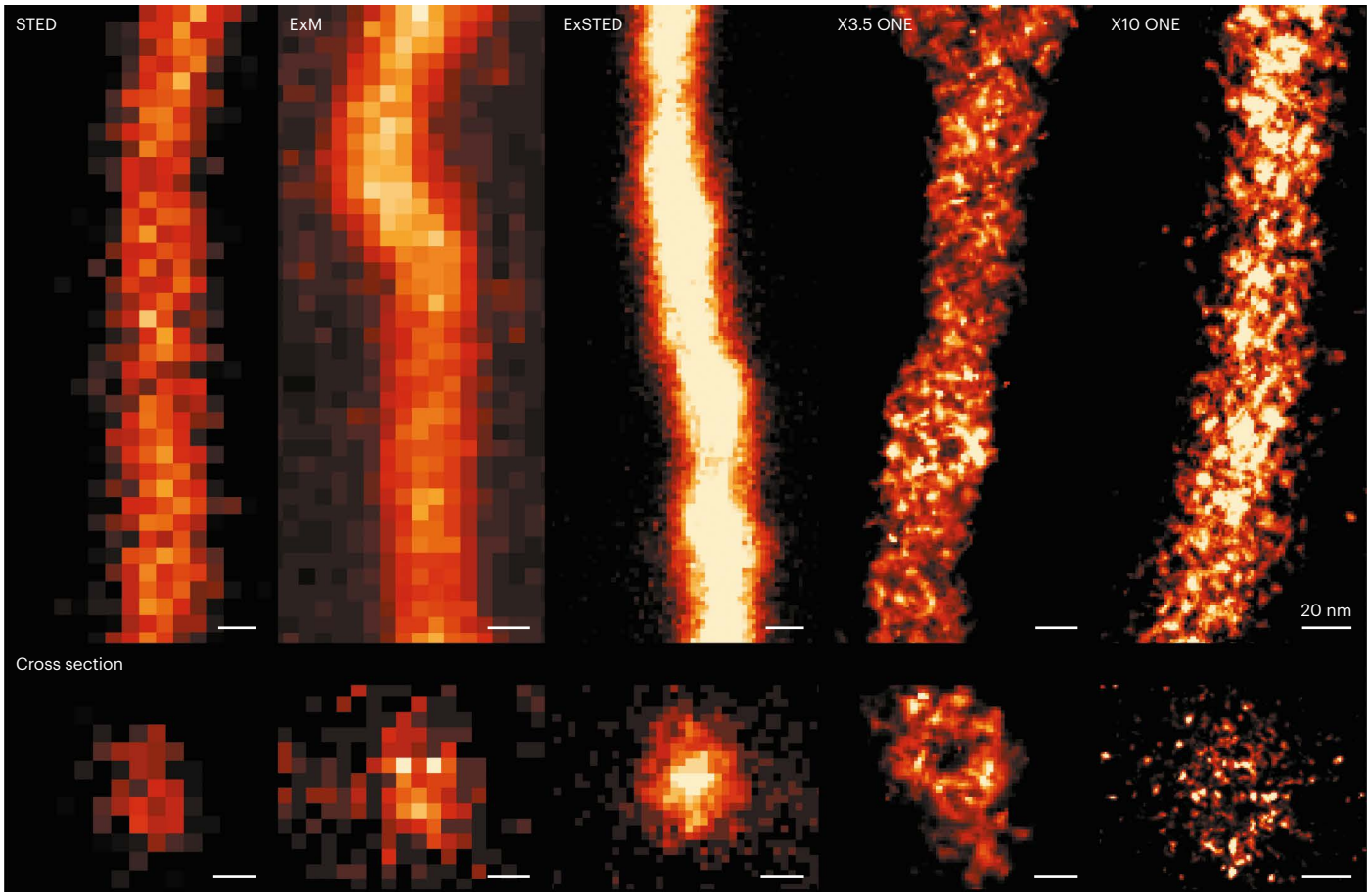
News in focus



ALI SHAIB *ET AL.*/BIORXIV (CC-BY-NC-ND 4.0)

The protein tubulin imaged by existing super-resolution and expansion microscopy methods (panels 1–3) and by ONE microscopy.

'DEMOCRACY IN MICROSCOPY': CHEAP LIGHT MICROSCOPE DELIVERS SUPER-RESOLUTION IMAGES

Technique pushes the instruments to beat the resolving power of multimillion-dollar machines.

By Ewen Callaway

When Ali Shaib was doing his master's degree at the Lebanese University in Beirut, he spent several weeks on a waiting list and visited a different campus to take a few images on a costly microscope, something scholars in richer countries took for granted.

Now, Shaib, a nanoscale specialist at the University Medical Center Göttingen in Germany, and his colleagues have developed a method using ordinary light microscopes that they hope will demolish such barriers.

The technique — which has recorded jaw-dropping images of individual proteins and never-before-seen structures in cells — offers a level of detail that eclipses even that of multimillion-dollar 'super-resolution' microscopes (A. H. Shaib *et al*. Preprint at bioRxiv https://doi.org/jxmc; 2023).

"There should be some form of democracy in microscopy," says Silvio Rizzoli, a nanoscale specialist also at the University Medical Center Göttingen who has pioneered the technique, dubbed ONE microscopy, with Shaib. "It's high resolution for the many, not the few rich labs."

The power of conventional light microscopes is limited by the laws of optics, which mean that objects smaller than about 200 nanometres can be seen only as a blur using visible light. But researchers have previously developed physics-beating super-resolution methods that, Rizzoli says, can bring this limit down to around 10 nm. The approach, which earned the 2014 Nobel Prize in Chemistry, uses optical tricks to pinpoint fluorescent molecules attached to proteins.

In 2015, researchers reported another way to evade optical limits. A team led by Edward Boyden, a neuroengineer at the Massachusetts Institute of Technology in Cambridge, showed that inflating tissue — with the help of an absorbent compound used in nappies — moves cellular objects away from each other (F. Chen *et al*. *Science* **347**, 543–548; 2015). This technique, called expansion microscopy, led to leaps in microscope resolution and can resolve structures down to around 20 nm.

Shaib and Rizzoli's technique — described in a study posted to the bioRxiv preprint server last month — melds the two approaches to achieve resolutions below 1 nm. That is sharp enough to reveal the shapes of individual proteins, which are typically imaged in finer detail using much more expensive structural-biology methods such as cryo-electron microscopy (cryo-EM) or X-ray crystallography.

Expansion microscopy's simplicity is part of its appeal, says Boyden, who estimates that more than 1,000 laboratories have adopted the technique. Samples are treated with chemicals that anchor their proteins to a polymer that, with the addition of water, swells to 1,000 times its original size, moving the molecules apart. ONE (short for one-step nanoscale-expansion) microscopy uses heat or enzymes to also break the proteins apart, so that individual fragments are stretched in different directions during expansion.

The researchers have used their approach to record pictures of a neural molecule, the $GABA_A$ receptor, that closely resemble much-higher-resolution cryo-EM and X-ray crystallography maps of the protein. They have also captured the outlines of a bulky protein called otoferlin that helps to convey audio signals in the brain , for which the structure hasn't been determined. The shape resembles a structural prediction made by the AlphaFold deep-learning network.

The method cannot match the resolution of cryo-EM, which in some cases can reveal near-atomic-level details smaller than 0.2 nm. But cryo-EM can be finnicky and expensive. By contrast, ONE microscopy could offer a quick and easy way to obtain structural insights into just about any molecule, says Rizzoli. "You can look at any protein, and you can get resolution you couldn't dream about."

Increased accessibility

Rizzoli says that part of the motivation for developing the technique was to broaden the accessibility of cutting-edge light microscopy. The ONE-microscopy method is straightforward to apply and works with now-antiquated fluorescent microscopes from the 1990s.

Salma Tammam, a pharmaceutical technologist at the German University in Cairo, is planning to send a PhD student to Göttingen to learn the technique this summer. Her lab studies how nanoparticles move about in cells. The team would like to see the fine details of the particles and their cargo. But like many researchers in low and middle-income countries, they do not have access to expensive super-resolution microscopes. "This brings us resolution in an affordable manner," she says.

Broadening the reach of super-resolution microscopy is also important for scientists at well-funded institutions, says Noa Lipstein, a synapse biologist at Leibniz Center for Molecular Pharmacology in Berlin. She has access to a well-established super-resolution technique called stimulated emission depletion microscopy. But she has chosen to apply ONE microscopy to her research into the fine details of neural synapses.

"It's allowed me independence, because I don't have to rely on connections to big shots with heavy machines," Lipstein says. "This I can do in my own lab and my own bench."

Lipstein hasn't pushed the technique to its limits, but she's already getting glimpses of new biology. "It's almost a given that we are going to see new things. We already see them, but we don't know what they are," she says.

SCHOLARS DECRY FUNDING BAN FOR INDIAN RESEARCH CENTRE

The Centre for Policy Research conducts some of the country's most influential policy studies.

By Dyani Lewis

International researchers fear long-standing collaborations with Indian researchers might be imperilled by a decision by the Indian government to suspend foreign funding for the Centre for Policy Research (CPR), a think tank in New Delhi. Research projects at the CPR — which conducts some of India's most influential independent policy studies — have been paused temporarily after the Indian Ministry of Home Affairs suspended the think tank's government licence to receive overseas funds for 180 days or until further notice.

The move sparked an outcry among researchers, who are concerned that the funding pause could hobble the CPR and muzzle independent scrutiny of policy in India, which some say is threatened by Prime Minister Narendra Modi's government.

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The effects of climate change are among the topics studied at the centre.

"CPR cannot survive in its present shape," says political scientist Christophe Jaffrelot at the French national research centre CNRS in Paris. Jaffrelot fears that the suspension will remain in place indefinitely and could spell the end of the think tank.

"This government action will scare away even potential domestic funders," says Vinay Sitapati, a political scientist at Ashoka University in Rajiv Gandhi Education City near Delhi.

The CPR conducts research into public policy in fields including climate change, social and economic policy, governance and infrastructure. Last year, it received about three-quarters of its grant funding from global organizations such as the Bill & Melinda Gates Foundation and the World Bank. Its domestic researchers have contributed to high-profile international studies such as reports by the Intergovernmental Panel on Climate Change.

"A permanent suspension — or rather cancellation — would result in a significant loss in available resources to undertake our research work and fulfil our institutional mandate," a CPR official told *Nature*.

The suspension relates to the CPR's registration to the Foreign Contribution (Regulation) Act, which is designed to ensure that foreign entities do not unduly influence Indian domestic politics. The law was amended by Modi's government in 2020 to increase government powers to regulate and scrutinize foreign payments to organizations. The Ministry of Home